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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/819,464	03/28/2001	Martin Friede	B45070-1	1150

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EXAMINER	
LUCAS, ZACHARIAH	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 08/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/819,464	FRIEDE ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *74-73* is/are pending in the application.

4a) Of the above claim(s) *85-93* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *74-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 08/945,450, and 09/269,383.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. In the prior action, mailed on May 17, 2005, claims 74-93 were pending and subject to a requirement for restriction/election.

2. Applicant's election of Group I (compositions comprising an antigen, a sterol, and a saponin), embodiments wherein the antigen is a Plasmodium antigen, and species wherein the metal is aluminum in the reply filed on June 10, 2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. In the prior action on the merits, mailed on September 22, 2004, claims 47, 48, and 50-73 were pending and under consideration. These claims were cancelled in the submission of April 13, 2005, and replaced by new claims 74-93, which were subject to the May 2005 restriction requirement.

Of these pending claims, claims 74-84 are under consideration.

Claim Objections

4. **(Prior Objection- Withdrawn)** Previously pending claims 62, 63, 70, and 71 were objected to because of the following informalities: these claims refer to a compound (3D-MPL) by its complete name (3 De-O-acylated monophosphoryl lipid A). In view of the cancellation of these claims, and the inclusion of the full name of the compound in the newly added claims, the objection is withdrawn.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. **(Prior Rejection- Withdrawn)** Previously pending claims 47 and 48 were rejected under 35 U.S.C. 112, second paragraph, in the prior action as being indefinite because of the language "addition of excess sterol to the adjuvant formulation (weight/weight)." The claim was rejected because it was unclear if the determination of the excess is based upon the comparative weights of the saponin and the sterol, or upon the weights of the saponin and the formulation containing the saponin. These claims have been cancelled from the application. Additionally, the newly added claims have been drafted to clarify that the excess by weight of sterol is measured with respect to the saponin. In view of the amendments to the claims, the rejection is withdrawn.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. **(Prior Rejection- Restated)** Claims 47, 48, 50, 51, 56-59, 64-69, 72, and 73 were rejected under 35 U.S.C. 103(a) as being unpatentable over Lipford in view of the teachings of Kensil. These claims have been cancelled from the application. However, new claims 74-76, 78, 80, 82, and 83 describe compositions comprising an antigen, the saponin QS-21, and sterol (preferably cholesterol) in an excess by weight to the saponin of 1:2 to 1:100. Claims 78 and 80 further require the presence of either aluminum hydroxide or aluminum phosphate. Claim 83

requires that the sterol and saponin be in the form of a vesicle like structure. The limitations of the compositions of each of these claims are similar to the limitations required by the methods of the cancelled claims. New claim 84 identifies a specific antigen (here, Plasmodium antigen) to be included in the composition. Thus, the rejection is restated such that new compound claims 74-76, 78, 80, and 82-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lipford in view of Kensil.

As was previously described, Lipford teaches the making of an immunogenic composition comprising 5mg of cholesterol and .4mg of Quil A. Abstract, page 74. Thus, the reference teaches a method of combining an excess of cholesterol to saponin formulation with a ration of about 1:12.5. The reference does not teach the use of purified QS-21.

Kensil teaches that QS-21 is component of Quil A with adjuvant properties comparable to or greater than Quil A (cols 6, and 22-23). Kensil also teaches that the purified saponins of the patent (including QS-21) showed adjuvant effects at lower dosages than the crude saponin extract (Quil A). Columns 3-4, and col. 6, lines 30-40. Further, the reference teaches that these purified saponins tend to be less toxic (have less hemolytic activity) than the Quil A extract. Columns 3-4, and column 20. Thus, the art provides several reasons for the substitution of QS-21 for Quil A in the compositions of Lipford. It would therefore have been obvious to those of ordinary skill in the art to substitute the purified saponins of Kensil, one of which is QS-21, for the crude Quil A extract used in Lipford.

It is noted that while the references do not teach the specific purity of QS-21, such would have been an obvious optimization of the claimed inventions, particularly in view of the teachings of Kensil indicating that the purified saponins are less toxic that the crude extract.

Thus, the limitation of new claim 82 (requiring 98% purity) is therefore an obvious optimization of the composition suggested by the Lipford and Kensil references.

In addition, the Lipford reference teaches that the adjuvant composition disclosed therein may be used to enhance the immune response against peptide antigens in general. Abstract. Kensil supports these teachings, and identifies examples of target antigens with which saponin adjuvants can be used. Column 10, lines 38-50. Among the examples of antigens identified by Kensil are antigens from a Plasmodium protozoan.

Further, those of ordinary skill in the art would have had a reasonable expectation of success in the combination. This is because Lipford states that there are two aspects of ISCOM important to their activity- the liposome structure and the adjuvant properties of Quil A. Page 78, second full paragraph. The teachings of Kensil indicate that the properties Lipford identified for Quil A are also indicative of adjuvant properties of saponins in general. Column 12, lines 21-30. Thus, Kensil suggests that the fractions of Quil A, including QS21, would have these properties. Because Kensi indicates that QS-21 would share the required properties with the crude Quil A extract, those of ordinary skill in the art would also have had a reasonable expectation of success in the substitution of QS-21 for Quil A in the liposomes of Lipford. The combined teachings of these references therefore render the indicated claims obvious.

9. **(Prior Rejection- Withdrawn)** Claims 52-55, 60, and 61 were rejected under 35 U.S.C. 103(a) as being unpatentable over either Lipford in view of Kensil as applied to claims 47, 48, 50, 51, 56-59, 64-69, 72, and 73 above, and further in view of Bonati et al. (U.S. Patent

4,101,652- of record in the IDS of March 2001). These claims have been cancelled from the application. The rejection is therefore withdrawn.

10. **(Prior Rejection- Restated)** Claims 62, 63, 70, and 71 were rejected under 35 U.S.C. 103(a) as being unpatentable over either Lipford in view of Kensil, and further in view of Prieels et al. (WO 94/00153). These claims have been cancelled. However, new claims 77, 79, and 81 have been added to the application, which claims describe a composition with similar limitations (i.e., they read on compositions of an antigen, saponin, and an excess of cholesterol, wherein the adjuvant formulation also comprises alum salts and/or 3 De-O-acylated monophosphoryl lipid A). Thus, the rejection is restated such that new claims 77, 79, and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Lipford in view of Kensil, and further in view of Prieels.

As described above, the teachings of Lipford and Kensil render obvious the compositions of claims 74-76, 78, 80, and 82-84. However, while Kensil indicates that the saponins disclosed therein may be used with other adjuvants, the reference does not specifically suggest the use of 3D-MPL. The teachings of the Prieels reference demonstrate a synergy in the use of both QS-21 and 3D-MPL as adjuvants. Whole document. In addition to combinations of QS-21 and 3DMPL, the reference also teaches the inclusion of aluminum salts. Pages 12-14. Thus, from these teachings, it would have been obvious to those in the art to include 3D-MPL, or 3D-MPL and an aluminum salt, in the liposome formulations comprising QS-21. Those in the art would have had a reasonable expectation of success in the combination based on the teachings in Prieels that such combinations would be effective.

Conclusion

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Z. Lucas
Patent Examiner

JAMES HOUSEL 8/8/05
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